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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/753,043	12/27/2000	Sujata Kale	UMIC:048US	9653

7590 04/04/2003

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EXAMINER	
WITZ, JEAN C	

ART UNIT	PAPER NUMBER
1651	15

DATE MAILED: 04/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/753,043	KALE ET AL.	
	Examiner	Art Unit	
	Jean C. Witz	1651	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30 and 35-38* is/are pending in the application.

4a) Of the above claim(s) *35-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Arguments

Applicant's arguments with respect to claims 1-30 and 38 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 19, 22-18 and 38 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Van Blitterswijk et al. (U.S. Patent 6,152,964).

The patent discloses the culture of bone precursor cells to form what the patent calls mineralized "globular structures" or "nodules". The cellular and extracellular matrix in the nodules have similar morphological and ultrastructural characteristics to bone tisse. The cells associated with the nodules stain positive for alkaline phosphatase activity, and are Von Kossa positive for phosphate and alizarin red positive for calcium. Collagen fibers resembling collagen type I are present in the bone nodules. The

nodules contain bone-specific proteins such as osteopontin and osteocalcin. Finally, mineralization is composed of needle-shaped bone-like crystals.

Absent objective evidence of a side-by-side comparison, these disclosed nodules or globular structures are identical to those structures described by Applicants as "bone spheroids." Applicants identify their bone spheroids as rounded structures containing type I collagen, are positive for alkaline phosphatase, and are positive for alizarin red and have crystalline bone structures called microspicules. Review of Figure 1 of Applicants' specification and Figure 1 and 4 of the patent show similar structures.

The patent teaches that these structures are cultured and subsequently implanted in vivo for the purpose of stimulating new bone growth and meet all of broadest reasonable interpretations of the limitations of the cited claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 and 17-18 are rejected under 35 U.S.C. 102(a) or (e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Van Blitterswijk et al. (U.S. Patent 6,152,964).

As discussed above, the claimed "bone spheroids" are deemed to be the same as the disclosed "nodules" or "globular structures".

Claim 1, step b) requires that the culture of the osteogenic or bone precursor cell be performed under serum free conditions in the presence of one or more osteogenic growth factors. The patent teaches at col. 3 suggests the use of conditioned medium from previous osteogenic or bone precursor cell culture such that the medium contains factors which are important for cell growth and cell differentiation. Dexamethasone, a synthetic glucocorticoid, is also added to induce proliferation and terminal differentiation of osteogenic cells. Further, the patent teaches at col. 5, line 14, that the fetal calf serum in the culture can be replaced by synthetic serum. This term has been interpreted to mean that culture can be performed in serum free medium insofar that a serum free medium is augmented with individual purified components known to be found in serum that is known to be required for mammalian cell culture instead of augmented with the relatively undefined composition of actual blood serum.

Step c) of claim 1 requires that the cultures are maintained at cell densities that allow the formation of a bone cell spheroid. Since both the specification and the

reference teach the same initial starting densities ($10^3 - 10^6$ cells per cm^2), and since bone cell spheroids are subsequently produced by the method of the reference, it is clear that this limitation is met by the patent's disclosure.

Claims 2-9 specify the origin of the osteogenic or bone precursor cell. The reference teaches at col. 3 that the cells can be allogenic or autologous. Rat and chick cells are specifically disclosed. Therefore, it is deemed inherent in the disclosure of the reference that all potential origins of bone cells are disclosed.

Finally, the limitations of claims 17-18 are met by the disclosure of the patent.

Therefore, the cited claims are deemed anticipated by the disclosure of the patent. In the alternative, the disclosure of the use of "synthetic serum" and the teaching of both allogenic and autologous cell sources would motivate one of ordinary skill in the art at the time the invention was made to select an appropriate serum free medium and the specific source of the cells for the practice of the claimed invention.

Claims 10-16, 20-22, 25, and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Blitterswijk et al. (U.S. Patent 6,152,964) in view of Long et al.

Claims 10-11 recite the specific growth factor. As stated above, the patent uses dexamethasone and/or conditioned medium which is known to contain growth factors. Long et al. specifies some of the known growth factors including transforming growth factor-beta, bone morphogenic proteins. All of the listed growth factors are acknowledged by Applicants to be known as bone stimulatory factors. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was

made to identify and include known bone growth stimulatory factors in the practice of the claimed method.

Claims 12-16 recite conventional cell separation/purification techniques. For example, Long uses density separation and immune-adherence techniques using antibodies to alkaline phosphatase. Therefore, it would have been obvious to one of ordinary skill in the art to use conventional cell separation/purification techniques to isolate osteogenic or bone precursor cells.

Claims 20-22 recite conventional implantation carriers. At col. 3, the patent discloses that numerous conventional implantation substrates can be used. The substrate is disclosed as being selected from a nonlimiting list including metal, a bioactive surface such as calcium phosphate, ceramics and polymer surfaces such a polyethylene and the like. The carrier materials listed in claims 20-22 all recite known polymer carriers as well as bioactive and inert substrates.

Claim 25 recites the use of these bone spheroids in plastic surgery. Claim 29 recites specific conditions to be treated. The patent details a virtually unlimited list of conditions associated with bone surgery in which the implants can be used. Plastic surgery encompasses a broad range of surgeries involved in improving the appearance of an individual. Such surgeries are disclosed and suggested by the patent; for example, at col. 4, the patent discloses the use of the composition for restoring mandible structure and for prosthetic surgery. This clearly motivates one of ordinary skill in the art to use the claimed invention to improve the physical appearance of a patient. Further, at col. 2, the patent teaches the use of the claimed invention for

reconstitution of bone defects and damaged or lost bone. The conditions recited in claim 29 result in damaged or lost bone. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to use the claimed invention in the treatment of any medical condition that is known to be characterized by damaged or lost bone.

Finally, claim 30 recites that the cells are removed prior to implantation. In Example 6 at col. 8, the extracellular matrix is isolated and the cells contained therein are specifically killed. See lines 35-40. That matrix is then used to culture further osteoblasts. The conclusion of the experiment indicated that the presence of this matrix can trigger the activity of and bone production of osteogenic cells. This would therefore motivate one of ordinary skill in the art to be able to use not only the cells and matrix together, but also the matrix alone with the expected improved bone stimulation and growth of endogenous osteoblasts at the site of implantation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jean C. Witz whose telephone number is (703) 308-3073. The examiner can normally be reached on 6:30 a.m. to 4:00 p.m. M-Th and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jean C. Witz
Primary Examiner
Art Unit 1651

April 2, 2003